Relations Between Polygenic Risk Scores of Internalizing and Externalizing Behaviors and Alcohol Use Disorder Symptoms

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Introduction

- Alcohol use disorder (AUD) arises from problematic patterns of alcohol use; endorsement of two or more of the eleven DSM-5 symptoms in a year prompts disagnosis.[1]
- Many disorders/traits are polygenic—many loci play a role in their manifestation. Polygenic risk scores (PRSs) assess this contribution as aggregate measures of genetic risk by summing weighted variants from genome-wide association studies (GWASs).[2]
- Internalizing (i.e., mood and anxiety disorders, neuroticism, and worry) and externalizing (i.e., oppositional behavior and social norm violation disorders, risk-taking, and aggression) behaviors are separable, though correlated, forms of psychopathology.[3,4,5]
- Prior studies have shown that some AUD symptoms are more reflective of externalizing pathology than others. For example, externalizing behavior is associated with social problems and role interference, but other AUD symptoms are associated by other symptomatology, which may include internalizing behaviors.[6]
- Thus, we hypothesize that genetic risk for internalizing and externalizing behaviors may differentially predict AUD symptoms.
- **<u>Aim of research:</u> To examine the predictive accuracy of polygenic risk scores for internalizing and externalizing behaviors to better understand the etiology of the individual AUD symptoms.**

Methods

GWASs (Discovery Samples) & Measures

- After survey procedures, individual genomic and phenotypic data were collected for GWAS analyses to identify single nucleotide polymorphisms influencing phenotypic display.
- **Risk-taking behavior:** n = 939,908.
  - Responses to the following item were obtained: "Would you describe yourself as someone who takes risks?"
  - Identified 124 loci associated with risk-tolerance.[7]
- **Neuroticism:** n = 449,484.
  - 12 Yes/No questions from the Eysenck Personality Questionnaire Revised Short Form were administered.
  - Identified 136 loci related to neuroticism.[8]
- **Aggression:** n = 18,988.
  - Child aggression assessed w/ 21 Child Behavior Checklist items.
  - Identified locus on 2p12 in chromosome 2 to be close to genome-wide significance and 5 other suggestive loci.[9]
- **Worry:** n = 348,219.
  - 4 Yes/No questions from the Eysenck Personality Questionnaire Revised Short Form specifically related to "worry" were scored prior to locating associated loci.
  - Identified 26 loci related to this sub-facet of neuroticism.[8]

UCSF Family Alcoholism Study (Target Sample)

- One person in each family (n = 2,154) met screening criterion of alcohol dependence during their lifetime and had a sibling or both parents to participate in interviews that assessed diagnoses for DSM-IV and ICD-10 alcohol dependence/abuse.[10]

Procedure

Figure 1. *Data Analysis Procedure*

1. Obtained discovery sample GWASs with derived summary statistics.

2. Retrieved UCSF target sample: DSM-5 alcohol use disorder symptom data.

<u>Our lab analyses begin here:</u>

3. PRSs for each UCSF participant were created from discovery summary statistics by summing alleles weighted by effect sizes using PRS-CS.[11]

4. Generalized logistic mixed models were used to examine significant associations ($p < 0.05$) between PRSs and AUD symptoms controlling for age and ancestry in the R package *pedigreemm*.[12,13]

GWAS Phenotypes	**Neuroticism (NEU)**	**Worry (WOR)**	**Risk-tolerance (RISK)**	**Aggression (AGG)**

AUD Symptoms	**Inability to Cut/Stop (CS)**	**Larger/Longer Amounts (LL)**	**Craving (CR)**	**Long Time Spent (TS)**	**Tolerance (TO)**	**Reduced Activities (RA)**
	Role Failure (RF)	**Withdrawal (WD)**	**Continued Use w/ Illness (CU)**	**Hazardous Use (HU)**	**Interpersonal Problems (IN)**	

Results

Table 1. *Modeling of individual PRSs for neuroticism, worry, risk-tolerance, and aggression predicting AUD symptoms*

	stat	CS	LL	CR	TS	TO	RA	RF	WD	CU	HU	IN
NEU	β	0.14 ± 0.05	0.16 ± 0.05	0.17 ± 0.05	0.13 ± 0.05	0.15 ± 0.05	0.12 ± 0.05	0.12 ± 0.05	0.14 ± 0.05	0.16 ± 0.05	0.09 ± 0.05	0.14 ± 0.05
	p	**0.00656**	**0.00217**	**0.00088**	**0.01023**	**0.00301**	**0.02037**	**0.01391**	**0.00491**	**0.00296**	0.09041	**0.00826**
	ΔR^2	0.0056	0.0076	0.0087	0.0046	0.0069	0.0039	0.0045	0.0058	0.0070	0.0021	0.0055
WOR	β	0.11 ± 0.05	0.09 ± 0.05	0.09 ± 0.05	0.05 ± 0.05	0.07 ± 0.05	0.09 ± 0.05	0.10 ± 0.05	0.08 ± 0.05	0.07 ± 0.05	0.03 ± 0.05	0.07 ± 0.05
	p	**0.02859**	0.07543	0.09422	0.28535	0.14936	0.07570	**0.04949**	0.12843	0.16711	0.57482	0.19875
	ΔR^2	0.0038	0.0026	0.0022	0.0008	0.0017	0.0025	0.0029	0.0017	0.0016	0.0002	0.0013
RISK	β	0.04 ± 0.05	0.02 ± 0.05	0.09 ± 0.05	0.04 ± 0.05	0.06 ± 0.05	0.08 ± 0.05	0.03 ± 0.05	-0.01 ± 0.05	0.05 ± 0.05	0.04 ± 0.05	0.05 ± 0.05
	p	0.39015	0.64822	0.09567	0.49853	0.28001	0.13774	0.57485	0.85157	0.34973	0.47792	0.33593
	ΔR^2	0.0006	0.0002	0.0023	0.0004	0.0010	0.0018	0.0003	0.00002	0.0007	0.0005	0.0008
AGG	β	0.15 ± 0.06	0.17 ± 0.06	0.15 ± 0.06	0.17 ± 0.06	0.18 ± 0.06	0.22 ± 0.06	0.11 ± 0.06	0.11 ± 0.06	0.16 ± 0.06	0.15 ± 0.06	0.16 ± 0.06
	p	**0.01076**	**0.00572**	**0.01034**	**0.00598**	**0.00263**	**0.00022**	0.06867	0.06018	**0.00954**	**0.01123**	**0.00960**
	ΔR^2	0.0052	0.0063	0.0054	0.0063	0.0072	0.0110	0.0026	0.0028	0.0055	0.0051	0.0054

- Significance level ($p < 0.05$).
- Neuroticism PRSs were significant for all AUD symptoms excluding hazardous use ($p = 0.09041$).
- Worry PRSs positively predicted cut/stop ($p = 0.02859$) and role failure ($p = 0.04949$) only.
- Aggression PRSs were significant for all symptoms but role failure and withdrawal (p's > 0.06).
- PRSs for risky behavior were not significant for any AUD symptom.
- Individual models explained 0.002%- 1.10% of variance.

Table 2. *Joint modeling of neuroticism and aggression PRSs predicting AUD symptoms*

	stat	CS	LL	CR	TS	TO	RA	RF	WD	CU	HU	IN
NEU & AGG	β	0.13 ± 0.05	0.15 ± 0.05	0.17 ± 0.05	0.13 ± 0.05	0.14 ± 0.05	0.11 ± 0.05	0.12 ± 0.05	0.14 ± 0.05	0.15 ± 0.05	0.08 ± 0.05	0.13 ± 0.05
	p	**0.01010**	**0.00361**	**0.00144**	**0.01591**	**0.00516**	**0.03516**	**0.01850**	**0.00678**	**0.00476**	0.12210	**0.01270**
	ΔR^2	0.0050	0.0069	0.0080	0.0040	0.0061	0.0032	0.0041	0.0053	0.0063	0.0018	0.0048
	β	0.14 ± 0.06	0.16 ± 0.06	0.14 ± 0.06	0.16 ± 0.06	0.17 ± 0.06	0.22 ± 0.06	0.10 ± 0.06	0.10 ± 0.06	0.15 ± 0.06	0.15 ± 0.06	0.15 ± 0.06
	p	**0.01660**	**0.00958**	**0.01748**	**0.00924**	**0.00448**	**0.00036**	0.09380	0.08607	**0.01549**	**0.01470**	**0.01470**
	ΔR^2	0.0046	0.0055	0.0047	0.0057	0.0065	0.0102	0.0022	0.0024	0.0048	0.0048	0.0048

- When included in a model together both the neuroticism PRSs and aggression PRSs remained significant for each AUD item in which they demonstrated main effects.
- The joint model explained 0.18%- 0.80% of variance.

Discussion

- Results demonstrated genetic risk for neuroticism and for aggression predicted eight of the same AUD symptoms.
  - Neuroticism positively predicted inability to cut-down usage, consuming larger/longer amounts, craving, long time spent consuming, higher tolerance, reduced activities, role failure, withdrawal, continued use despite mental health problems, and using despite interpersonal problems.
  - Aggression predicted the same symptoms, excluding role failure and withdrawal, and also predicted hazardous use.
- Genetic risk for worry predicted inability to cut down and role failure; risk-taking predicted no symptoms.
- Joint models including the neuroticism and aggression PRSs suggested that each PRS was predicting unique variance for each AUD symptom.
- These findings suggest that genetic risk for internalizing and externalizing behaviors show similar relations with most AUD symptoms but these relations are independent of each other. This is contrary to our original hypothesis that internalizing and externalizing genetic risk would influence distinct subsets of AUD symptoms.

Future Directions

- The influence of sex as a covariate and moderator should be examined in future studies to evaluate its impact on relations between internalizing and externalizing behaviors and AUD symptoms.
- PRSs only account for genetic influence. Future studies should focus on how social environments interact with genetics to influence AUD.
- Despite the largely null results for PRSs of risk-taking and worry, these relations should be explored further as more extensive phenotyping of "risk-taking" and "worry" may result in more accurate GWASs.

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